Clinical trial results:
A Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2

Summary

EudraCT number	2017-000693-11
Trial protocol	BE DK FI HU NL FR
Global end of trial date	21 September 2023

Results information

Result version number	v1
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	8616-169

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03909165
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2023
Global end of trial reached?	Yes
Global end of trial date	21 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy, safety, and pharmacokinetics (PK) of sugammadex (MK-8616) for reversal of both moderate and deep neuromuscular blockade (NMB) in pediatric participants aged birth to <2 years. The primary hypothesis of this study was that sugammadex was superior to neostigmine in reversing moderate NMB as measured by time to neuromuscular recovery.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	145
EEA total number of subjects	40

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	29
Infants and toddlers (28 days-23 months)	116
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

145 pediatric participants between the ages of birth and <2 years undergoing a procedure requiring a neuromuscular blocking agent (NMBA) for either moderate or deep block were enrolled in this study. Participants were enrolled in 4 age cohorts: birth to 27 days, 28 days to <3 months, 3 months to <6 months, and 6 months to <2 years.

Pre-assignment

Screening details:

50 participants were allocated to moderate block and reversal (2 mg/kg) or deep block and reversal (4 mg/kg) with sugammadex in Part A. 95 participants were randomized in Part B to moderate block and reversal (2 mg/kg) with sugammadex, deep block and reversal (4 mg/kg) with sugammadex, or moderate block and reversal with neostigmine (50 µg/kg).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Assessor, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Sugammadex 2 mg/kg

Arm description:

Participants received a single intravenous (IV) bolus of sugammadex at 2 mg/kg for moderate NMB reversal.

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616 Bridion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per allocation (Part A)/randomization (Part B) in a single IV bolus at 2 mg/kg within 2 minutes of the reappearance of a second twitch (T2) in response to train-of-four (TOF) stimulations for moderate NMB reversal, or in a single IV bolus at 4 mg/kg after final dose of NMBA (rocuronium or vecuronium) within 2 minutes of detection of a target of 1 to 2 post-tetanic counts and no response to TOF stimulations (TOF=0) for deep NMB reversal.

Arm title	Part A: Sugammadex 4 mg/kg

Arm description:

Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616 Bridion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per allocation (Part A)/randomization (Part B) in a single IV bolus at 2 mg/kg within 2 minutes of the reappearance of a second twitch (T2) in response to train-of-four (TOF) stimulations for moderate NMB reversal, or in a single IV bolus at 4 mg/kg after final dose of NMBA (rocuronium or

vecuronium) within 2 minutes of detection of a target of 1 to 2 post-tetanic counts and no response to TOF stimulations (TOF=0) for deep NMB reversal.

Arm title	Part B: Sugammadex 2 mg/kg

Arm description:

Participants received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616 Bridion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per allocation (Part A)/randomization (Part B) in a single IV bolus at 2 mg/kg within 2 minutes of the reappearance of a second twitch (T2) in response to train-of-four (TOF) stimulations for moderate NMB reversal, or in a single IV bolus at 4 mg/kg after final dose of NMBA (rocuronium or vecuronium) within 2 minutes of detection of a target of 1 to 2 post-tetanic counts and no response to TOF stimulations (TOF=0) for deep NMB reversal.

Arm title	Part B: Sugammadex 4 mg/kg

Arm description:

Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616 Bridion
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per allocation (Part A)/randomization (Part B) in a single IV bolus at 2 mg/kg within 2 minutes of the reappearance of a second twitch (T2) in response to train-of-four (TOF) stimulations for moderate NMB reversal, or in a single IV bolus at 4 mg/kg after final dose of NMBA (rocuronium or vecuronium) within 2 minutes of detection of a target of 1 to 2 post-tetanic counts and no response to TOF stimulations (TOF=0) for deep NMB reversal.

Arm title	Part B: Neostigmine + (Glycopyrrolate or Atropine)

Arm description:

Participants received a single IV bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) in combination with either glycopyrrolate (10 µg/kg) or atropine sulfate (20 µg/kg) based on availability and/or contraindications, for moderate NMB reversal.

Arm type	Active comparator
Investigational medicinal product name	Neostigmine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

For moderate NMB reversal, a single IV. bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) with either glycopyrrolate or atropine was given after final dose of NMBA (rocuronium or vecuronium) and within 2 minutes of the reappearance of T2 in response to TOF stimulations.

Investigational medicinal product name	Atropine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atropine (20 ug/kg) administered in a single IV. bolus with neostigmine (50 µg/kg; up to 5 mg maximum dose) after final dose of NMBA (rocuronium or vecuronium) and within 2 minutes of the reappearance of T2 in response to TOF stimulations.

Investigational medicinal product name	Glycopyrrolate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Glycopyrrolate (10 ug/kg) administered in a single IV. bolus with neostigmine (50 µg/kg; up to 5 mg maximum dose) after final dose of NMBA (rocuronium or vecuronium) and within 2 minutes of the reappearance of T2 in response to TOF stimulations.

Number of subjects in period 1	Part A: Sugammadex 2 mg/kg	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg
Started	16	34	31
Treated	15	32	29
Completed	15	31	29
Not completed	1	3	2
Physician decision	-	1	-
Consent withdrawn by subject	-	2	1
Previous Drug Exposure	-	-	1
Randomized By Mistake Without Study Treatment	-	-	-
Early Discharge	1	-	-

Number of subjects in period 1	Part B: Sugammadex 4 mg/kg	Part B: Neostigmine + (Glycopyrrolate or Atropine)
Started	32	32
Treated	31	31
Completed	31	31
Not completed	1	1
Physician decision	-	-
Consent withdrawn by subject	1	-
Previous Drug Exposure	-	-
Randomized By Mistake Without Study Treatment	-	1
Early Discharge	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Sugammadex 2 mg/kg
Reporting group description:	
Participants received a single intravenous (IV) bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Reporting group title	Part A: Sugammadex 4 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Reporting group title	Part B: Sugammadex 2 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Reporting group title	Part B: Sugammadex 4 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Reporting group title	Part B: Neostigmine + (Glycopyrrolate or Atropine)
Reporting group description:	
Participants received a single IV bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) in combination with either glycopyrrolate (10 µg/kg) or atropine sulfate (20 µg/kg) based on availability and/or contraindications, for moderate NMB reversal.	

Reporting group values	Part A: Sugammadex 2 mg/kg	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg
Number of subjects	16	34	31
Age Categorical Units: Subjects			
Newborns (0-27 days)	4	6	7
Infants and toddlers (28 days-23 months)	12	28	24
Age Continuous Units: days			
arithmetic mean	195.9	140.1	157.9
standard deviation	± 193.4	± 121.7	± 171.8
Gender Categorical Units: Subjects			
Female	7	13	5
Male	9	21	26
Race Units: Subjects			
American Indian Or Alaska Native	0	2	4
Asian	2	4	6
Black Or African American	0	0	0
Multiple	0	0	0
White	14	28	21
Ethnicity Units: Subjects			
Hispanic Or Latino	3	6	10
Not Hispanic Or Latino	13	28	21
Not Reported	0	0	0

Reporting group values	Part B: Sugammadex 4 mg/kg	Part B: Neostigmine + (Glycopyrrolate or Atropine)	Total
Number of subjects	32	32	145
Age Categorical Units: Subjects			
Newborns (0-27 days)	6	6	29
Infants and toddlers (28 days-23 months)	26	26	116
Age Continuous Units: days			
arithmetic mean	169.1	174.3	
standard deviation	± 165.5	± 192.7	-
Gender Categorical Units: Subjects			
Female	11	12	48
Male	21	20	97
Race Units: Subjects			
American Indian Or Alaska Native	1	4	11
Asian	8	8	28
Black Or African American	2	1	3
Multiple	1	2	3
White	20	17	100
Ethnicity Units: Subjects			
Hispanic Or Latino	7	9	35
Not Hispanic Or Latino	24	23	109
Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Part A: Sugammadex 2 mg/kg
Reporting group description:	
Participants received a single intravenous (IV) bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Reporting group title	Part A: Sugammadex 4 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Reporting group title	Part B: Sugammadex 2 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Reporting group title	Part B: Sugammadex 4 mg/kg
Reporting group description:	
Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Reporting group title	Part B: Neostigmine + (Glycopyrrolate or Atropine)
Reporting group description:	
Participants received a single IV bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) in combination with either glycopyrrolate (10 µg/kg) or atropine sulfate (20 µg/kg) based on availability and/or contraindications, for moderate NMB reversal.	
Subject analysis set title	Part A: Sugammadex 2 mg/kg [birth to 27 days]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged birth to 27 days received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Subject analysis set title	Part A: Sugammadex 2 mg/kg [28 days to <3 months]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 28 days to <3 months received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Subject analysis set title	Part A: Sugammadex 2 mg/kg [3 to < 6 months]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 3 to < 6 months received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Subject analysis set title	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 6 months to < 2 years received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.	
Subject analysis set title	Part A: Sugammadex 4 mg/kg [birth to 27 days]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged birth to 27 days received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Subject analysis set title	Part A: Sugammadex 4 mg/kg [28 days to <3 months]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 28 days to <3 months received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.	
Subject analysis set title	Part A: Sugammadex 4 mg/kg [3 to < 6 months]
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 3 to < 6 months received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Subject analysis set title	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants aged 6 months to < 2 years received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Subject analysis set title	Parts A + B: Sugammadex 2 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in Parts A and B received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.

Subject analysis set title	Parts A + B: Sugammadex 4 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in Parts A and B received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Subject analysis set title	Part B: Neostigmine + (Glycopyrrolate or Atropine)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received a single IV bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) in combination with either glycopyrrolate (10 µg/kg) or atropine sulfate (20 µg/kg) based on availability and/or contraindications, for moderate NMB reversal.

Primary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0-inf) for Sugammadex

End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0-inf) for Sugammadex

End point description:

Pharmacokinetic (PK) blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine AUC0-inf for sugammadex. As pre-specified by the Statistical Analysis Plan (SAP) for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% confidence interval (CI) was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: Hour (hr)*ug/mL				
geometric mean (confidence interval 95%)	13.40 (0000 to 9999)	16.22 (12.14 to 21.67)	11.50 (8.61 to 15.37)	14.07 (11.24 to 17.61)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	8	5
Units: Hour (hr)*ug/mL				
geometric mean (confidence interval 95%)	39.09 (31.85 to 47.98)	31.90 (25.99 to 39.16)	24.75 (20.73 to 29.56)	27.75 (22.17 to 34.74)

Statistical analyses

Statistical analysis title	2 mg/kg AUC0-inf GMR 1
Statistical analysis description: 2 mg/kg AUC0-inf Geometric Mean Ratio (GMR) = Birth to 27 days AUC0-inf Geometric Mean (GM) / 28 days to < 3 months AUC0-inf GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [birth to 27 days] v Part A: Sugammadex 2 mg/kg [28 days to <3 months]
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.56
upper limit	1.21

Statistical analysis title	2 mg/kg AUC0-inf GMR 2
Statistical analysis description: 2 mg/kg AUC0-inf GMR = 28 days to < 3 months AUC0-inf GM / 3 to < 6 months AUC0-inf GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [28 days to <3 months] v Part A: Sugammadex 2 mg/kg [3 to < 6 months]
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.41
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.98

Statistical analysis title	4 mg/kg AUC0-inf GMR 3
Statistical analysis description: 4 mg/kg AUC0-inf GMR = 3 to < 6 months AUC0-inf GM / 6 months to < 2 years AUC0-inf GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [3 to < 6 months] v Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.13

Statistical analysis title	4 mg/kg AUC0-inf GMR 1
Statistical analysis description: 4 mg/kg AUC0-inf GMR = Birth to 27 days AUC0-inf GM / 28 days to < 3 months AUC0-inf GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [birth to 27 days] v Part A: Sugammadex 4 mg/kg [28 days to <3 months]
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.56

Statistical analysis title	4 mg/kg AUC0-inf GMR 2
Statistical analysis description: 4 mg/kg AUC0-inf GMR = 28 days to < 3 months AUC0-inf GM / 3 to < 6 months AUC0-inf GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [28 days to <3 months] v Part A: Sugammadex 4 mg/kg [3 to < 6 months]

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.03
upper limit	1.62

Statistical analysis title	2 mg/kg AUC0-inf GMR 3

Statistical analysis description:

2 mg/kg AUC0-inf GMR =
3 to < 6 months AUC0-inf GM / 6 months to < 2 years AUC0-inf GM.

Comparison groups	Part A: Sugammadex 2 mg/kg [3 to < 6 months] v Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6
upper limit	1.11

Primary: Part A: Area Under the Plasma Concentration Time Curve up to the Interpolated Concentration at 1 Hour Post Dose (AUC0-1hr) for Sugammadex

End point title	Part A: Area Under the Plasma Concentration Time Curve up to the Interpolated Concentration at 1 Hour Post Dose (AUC0-1hr) for Sugammadex

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine AUC0-1hr for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	6
Units: hr*ug/mL				
geometric mean (confidence interval 95%)	6.95 (5.38 to 8.99)	7.63 (5.90 to 9.87)	6.10 (4.72 to 7.88)	7.31 (6.09 to 8.76)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	7	9	7
Units: hr*ug/mL				
geometric mean (confidence interval 95%)	12.38 (10.33 to 14.85)	14.39 (12.16 to 17.02)	13.46 (11.61 to 15.61)	13.92 (11.76 to 16.46)

Statistical analyses

Statistical analysis title	2 mg/kg AUC0-1hr GMR 1
Statistical analysis description: 2 mg/kg AUC0-1hr GMR = Birth to 27 days AUC0-1hr GM / 28 days to < 3 months AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [birth to 27 days] v Part A: Sugammadex 2 mg/kg [28 days to <3 months]
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.67
upper limit	1.23

Statistical analysis title	2 mg/kg AUC0-1hr GMR 2
Statistical analysis description: 2 mg/kg AUC0-1hr GMR = 28 days to < 3 months AUC0-1hr GM / 3 to < 6 months AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [28 days to <3 months] v Part A: Sugammadex 2 mg/kg [3 to < 6 months]

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.69

Statistical analysis title	4 mg/kg AUC0-1hr GMR 2
Statistical analysis description:	
4 mg/kg AUC0-1hr GMR = 28 days to < 3 months AUC0-1hr GM / 3 to < 6 months AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [28 days to <3 months] v Part A: Sugammadex 4 mg/kg [3 to < 6 months]
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.89
upper limit	1.29

Statistical analysis title	4 mg/kg AUC0-1hr GMR 1
Statistical analysis description:	
4 mg/kg AUC0-1hr GMR = Birth to 27 days AUC0-1hr GM / 28 days to < 3 months AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [birth to 27 days] v Part A: Sugammadex 4 mg/kg [28 days to <3 months]
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.06

Statistical analysis title	4 mg/kg AUC0-1hr GMR 3
Statistical analysis description: 4 mg/kg AUC0-1hr GMR = 3 to < 6 months AUC0-1hr GM / 6 months to < 2 years AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [3 to < 6 months] v Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	1.17

Statistical analysis title	2 mg/kg AUC0-1hr GMR 3
Statistical analysis description: 2 mg/kg AUC0-1hr GMR = 3 to < 6 months AUC0-1hr GM / 6 months to < 2 years AUC0-1hr GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [3 to < 6 months] v Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.08

Primary: Part A: Area Under the Plasma Concentration Time Curve up to the Interpolated Concentration at 4 Hours Post Dose (AUC0-4hr) for Sugammadex

End point title	Part A: Area Under the Plasma Concentration Time Curve up to the Interpolated Concentration at 4 Hours Post Dose (AUC0-4hr) for Sugammadex[1]

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine AUC0-4hr for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% CI was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: hr*ug/mL				
geometric mean (confidence interval 95%)	10.68 (0000 to 9999)	13.99 (10.67 to 18.33)	10.13 (7.73 to 13.27)	12.57 (10.19 to 15.50)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	8	6
Units: hr*ug/mL				
geometric mean (confidence interval 95%)	27.79 (22.95 to 33.64)	27.16 (22.43 to 32.89)	21.51 (18.23 to 25.39)	22.43 (18.52 to 27.15)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Maximum Plasma Concentration (Cmax) of Sugammadex

End point title	Part A: Maximum Plasma Concentration (Cmax) of Sugammadex

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine Cmax for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	6
Units: ug/mL				
geometric mean (confidence interval 95%)	19.59 (14.15 to 27.13)	21.18 (14.55 to 30.84)	19.39 (13.32 to 28.23)	20.99 (16.09 to 27.38)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	8	9	7
Units: ug/mL				
geometric mean (confidence interval 95%)	28.56 (21.89 to 37.25)	30.38 (24.13 to 38.24)	44.51 (35.83 to 55.29)	40.86 (31.95 to 52.25)

Statistical analyses

Statistical analysis title	2 mg/kg Cmax GMR 1
Statistical analysis description: 2 mg/kg Cmax GMR = Birth to 27 days Cmax GM / 28 days to < 3 months Cmax GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [birth to 27 days] v Part A: Sugammadex 2 mg/kg [28 days to <3 months]
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.61
upper limit	1.4

Statistical analysis title	2 mg/kg Cmax GMR 2
Statistical analysis description: 2 mg/kg Cmax GMR = 28 days to < 3 months Cmax GM / 3 to < 6 months Cmax GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [28 days to <3 months] v Part A: Sugammadex 2 mg/kg [3 to < 6 months]

Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.7

Statistical analysis title	4 mg/kg Cmax GMR 3
Statistical analysis description:	
4 mg/kg AUC0-1hr GMR = 3 to < 6 months Cmax GM / 6 months to < 2 years Cmax GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [3 to < 6 months] v Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.43

Statistical analysis title	4 mg/kg Cmax GMR 1
Statistical analysis description:	
4 mg/kg Cmax GMR = Birth to 27 days Cmax GM / 28 days to < 3 months Cmax GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [birth to 27 days] v Part A: Sugammadex 4 mg/kg [28 days to <3 months]
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.26

Statistical analysis title	4 mg/kg Cmax GMR 2
Statistical analysis description: 4 mg/kg Cmax GMR = 28 days to < 3 months Cmax GM / 3 to < 6 months Cmax GM.	
Comparison groups	Part A: Sugammadex 4 mg/kg [28 days to <3 months] v Part A: Sugammadex 4 mg/kg [3 to < 6 months]
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	0.89

Statistical analysis title	2 mg/kg Cmax GMR 3
Statistical analysis description: 2 mg/kg Cmax GMR = 3 to < 6 months Cmax GM / 6 months to < 2 years Cmax GM.	
Comparison groups	Part A: Sugammadex 2 mg/kg [3 to < 6 months] v Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio (GMR)
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	1.36

Primary: Part A: Plasma Clearance (CL) of Sugammadex

End point title	Part A: Plasma Clearance (CL) of Sugammadex[2]

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine CL for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% CI was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: Liters/hour				
geometric mean (confidence interval 95%)	0.43 (0000 to 9999)	0.66 (0.47 to 0.92)	1.28 (0.91 to 1.80)	1.34 (1.03 to 1.74)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	8	5
Units: Liters/hour				
geometric mean (confidence interval 95%)	0.35 (0.28 to 0.45)	0.61 (0.48 to 0.78)	0.97 (0.79 to 1.19)	1.27 (0.98 to 1.65)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Apparent Volume of Distribution (Vd) for Sugammadex

End point title	Part A: Apparent Volume of Distribution (Vd) for

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine Vd for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% CI was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: Liters (L)				
geometric mean (confidence interval 95%)	1.14 (0000 to 9999)	1.45 (1.06 to 1.98)	2.68 (1.96 to 3.67)	2.70 (2.11 to 3.44)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	8	5
Units: Liters (L)				
geometric mean (confidence interval 95%)	1.22 (0.98 to 1.52)	1.35 (1.08 to 1.68)	2.16 (1.78 to 2.62)	2.77 (2.17 to 3.53)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution at Steady State (Vss) for Sugammadex

End point title	Apparent Volume of Distribution at Steady State (Vss) for Sugammadex[4]

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine Vss for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% CI was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: Liters (L)				
geometric mean (confidence interval 95%)	1.04 (0000 to 9999)	1.23 (0.94 to 1.60)	2.07 (1.59 to 2.70)	2.14 (1.74 to 2.63)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	8	5
Units: Liters (L)				
geometric mean (confidence interval 95%)	1.11 (0.92 to 1.34)	1.18 (0.98 to 1.43)	1.69 (1.43 to 1.98)	2.18 (1.77 to 2.68)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Half-Life (t1/2) of Sugammadex in Plasma

End point title	Part A: Half-Life (t1/2) of Sugammadex in Plasma[5]

End point description:

PK blood samples were collected in Part A from pediatric participants at multiple collection times post administration of sugammadex using a sparse sampling approach and used to determine t½ for sugammadex. As pre-specified by the SAP for the PK analysis, all PK parameters were analyzed and reported by Part A age cohort (birth to <28 days, 28 days to <3 months, 3 to <6 months, and 6 to <24 months) for each dose (2 mg and 4 mg). Values of 0000 and 9999 indicate that a 95% CI was not estimated for n<3 due to insufficient data to support its calculation. All pediatric participants in Part A who received at least 1 dose of sugammadex and had at least 5 samples at the time points of interest were analyzed. Per protocol, Part B participants were not analyzed for PK.

End point type	Primary

End point timeframe:

Day 1: 2, 15, 30, 60, 240 to 360, and 600 to 720 minutes post-dose

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Part A: Sugammadex 2 mg/kg [birth to 27 days]	Part A: Sugammadex 2 mg/kg [28 days to <3 months]	Part A: Sugammadex 2 mg/kg [3 to < 6 months]	Part A: Sugammadex 2 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	3	5
Units: Hours (h)				

geometric mean (geometric coefficient of variation)	1.84 (± 9999)	1.52 (± 20.21)	1.45 (± 28.57)	1.40 (± 24.25)

End point values	Part A: Sugammadex 4 mg/kg [birth to 27 days]	Part A: Sugammadex 4 mg/kg [28 days to <3 months]	Part A: Sugammadex 4 mg/kg [3 to < 6 months]	Part A: Sugammadex 4 mg/kg [6 months to < 2 years]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	9	5
Units: Hours (h)				
geometric mean (geometric coefficient of variation)	2.39 (± 27.34)	1.53 (± 16.42)	1.51 (± 28.79)	1.51 (± 19.46)

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Time to Neuromuscular Recovery (TTNMR)

End point title	Part B: Time to Neuromuscular Recovery (TTNMR)

End point description:

Time to neuromuscular recovery was defined as the interval from administration of reversal agent to time to neuromuscular recovery. TTNMR could be assessed by 1 of 4 methods selected by the investigator, based on their judgment of what was technically feasible and clinically appropriate for the participant's procedure. These methods were inclusive of both clinical signs (head lift or hip flexion) and neuromuscular transmission monitoring using either a standard peripheral nerve stimulator or the technically challenging quantitative neuromuscular monitoring to train-of-four (TOF) ratio ≥0.9. As pre-specified by the protocol and SAP, TTNMR was analyzed only in Part B participants under the setting of moderate block for comparison of sugammadex 2 mg to neostigmine. All participants in Part B who received either sugammadex 2 mg/kg or neostigmine and with available TTNMR data were analyzed.

End point type	Primary

End point timeframe:

Within Day 1

End point values	Part A: Sugammadex 2 mg/kg	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg	Part B: Sugammadex 4 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	29	0[8]
Units: Minutes				
median (confidence interval 95%)	(to)	(to)	1.4 (1.1 to 2.0)	(to)

Notes:

[6] - TTNMR was analyzed only in Part B under setting of moderate block.

[7] - TTNMR was analyzed only in Part B under setting of moderate block.

[8] - TTNMR was analyzed only in Part B under setting of moderate block.

End point values	Part B: Neostigmine + (Glycopyrrolate			

	or Atropine)			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Minutes				
median (confidence interval 95%)	4.4 (2.7 to 7.9)			

Statistical analyses

Statistical analysis title	Part B TTNMR

Statistical analysis description:

The Hazard Ratio (HR) for the pairwise comparison of Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine) was based on a Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous) and stratified by neuromuscular blocking agent.

Comparison groups	Part B: Sugammadex 2 mg/kg v Part B: Neostigmine + (Glycopyrrolate or Atropine)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	4.18

Notes:

[9] - Two-sided p-value based on log-rank test stratified by neuromuscular blocking agent and age groups.

Primary: Parts A and B: Percentage of Participants with Adverse Events (AEs) Up To 7 Days Post Administration of Study Medication

End point title	Parts A and B: Percentage of Participants with Adverse Events (AEs) Up To 7 Days Post Administration of Study Medication

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. As pre-specified by the protocol and SAP, the primary analysis of safety combined data across Part A and Part B (and across age cohorts) and included all AEs that occurred up to 7 days post administration of study medication. All enrolled/randomized participants from both Part A and Part B (combined) who received at least 1 dose of study treatment were analyzed and the percentage of participants with an AE was reported.

End point type	Primary

End point timeframe:

Up to Day 7

End point values	Parts A + B: Sugammadex 2 mg/kg	Parts A + B: Sugammadex 4 mg/kg	Part B: Neostigmine + (Glycopyrrolate or Atropine)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	44	63	31	
Units: Percentage of Participants				
number (not applicable)	68.2	68.3	61.3	

Statistical analyses

Statistical analysis title	Sugammadex 2 mg/kg vs. Neostigmine

Statistical analysis description:

The difference in percentage of sugammadex versus Neostigmine +plus (Glycopyrrolate or Atropine) was based on the Miettinen and Nurminen method stratified by neuromuscular blocking agent and age group.

Comparison groups	Parts A + B: Sugammadex 2 mg/kg v Part B: Neostigmine + (Glycopyrrolate or Atropine)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.2
upper limit	29.5

Statistical analysis title	Sugammadex 4 mg/kg vs. Neostigmine

Statistical analysis description:

The difference in percentage of sugammadex versus Neostigmine +plus (Glycopyrrolate or Atropine) was based on the Miettinen and Nurminen method stratified by neuromuscular blocking agent and age group.

Comparison groups	Parts A + B: Sugammadex 4 mg/kg v Part B: Neostigmine + (Glycopyrrolate or Atropine)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	26.7

Secondary: Part B: Time to Extubation

End point title	Part B: Time to Extubation

End point description:

Time to extubation was defined as the interval from administration of reversal agent to removal of the endotracheal tube. Monitoring of time to extubation was achieved using the Extubation Readiness Assessment, which evaluated and documented clinically relevant elements including neuromuscular recovery, mental status, return of spontaneous ventilation, adequate oxygenation, hemodynamically stabile, and core body temperature with “Yes”/”No” answers (no overall score or direction attributed). The Operating Room anesthesiologist or other trained personnel were responsible for assessing extubation readiness beginning about 1 minute after study treatment administration and reassessing every 60 seconds until time of extubation readiness was achieved.

End point type	Secondary

End point timeframe:

Within Day 1

End point values	Part A: Sugammadex 2 mg/kg	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg	Part B: Sugammadex 4 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	0[11]	29	0[12]
Units: Minutes				
median (confidence interval 95%)	(to)	(to)	7.9 (5.7 to 11.6)	(to)

Notes:

[10] - Time to Extubation was analyzed only in Part B under setting of moderate block.

[11] - Time to Extubation was analyzed only in Part B under setting of moderate block.

[12] - Time to Extubation was analyzed only in Part B under setting of moderate block.

End point values	Part B: Neostigmine + (Glycopyrrolate or Atropine)			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Minutes				
median (confidence interval 95%)	10.5 (7.9 to 13.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 14

Adverse event reporting additional description:

All-Cause Mortality includes all randomized participants. Serious adverse events (SAEs) and Nonserious AEs include all randomized participants who received ≥1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Part A: Sugammadex 2 mg/kg

Reporting group description:

Participants received a single intravenous (IV) bolus of sugammadex at 2 mg/kg for moderate NMB reversal.

Reporting group title	Part B: Neostigmine + (Glycopyrrolate or Atropine)

Reporting group description:

Participants received a single IV bolus containing neostigmine (50 µg/kg; up to 5 mg maximum dose) in combination with either glycopyrrolate (10 µg/kg) or atropine sulfate (20 µg/kg) based on availability and/or contraindications, for moderate NMB reversal.

Reporting group title	Part B: Sugammadex 4 mg/kg

Reporting group description:

Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Reporting group title	Part A: Sugammadex 4 mg/kg

Reporting group description:

Participants received a single IV bolus of sugammadex at 4 mg/kg for deep NMB reversal.

Reporting group title	Part B: Sugammadex 2 mg/kg

Reporting group description:

Participants received a single IV bolus of sugammadex at 2 mg/kg for moderate NMB reversal.

Serious adverse events	Part A: Sugammadex 2 mg/kg	Part B: Neostigmine + (Glycopyrrolate or Atropine)	Part B: Sugammadex 4 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	1 / 31 (3.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Anaesthetic complication			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device mechanical issue			

subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	3 / 29 (10.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Anaesthetic complication			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			

subjects affected / exposed	1 / 32 (3.13%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device mechanical issue			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A: Sugammadex 2 mg/kg	Part B: Neostigmine + (Glycopyrrolate or Atropine)	Part B: Sugammadex 4 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)	16 / 31 (51.61%)	17 / 31 (54.84%)

Injury, poisoning and procedural complications			
Post procedural oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Procedural vomiting			
subjects affected / exposed	2 / 15 (13.33%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Procedural pain			
subjects affected / exposed	7 / 15 (46.67%)	10 / 31 (32.26%)	13 / 31 (41.94%)
occurrences (all)	7	10	13
Procedural nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	3 / 31 (9.68%)	0 / 31 (0.00%)
occurrences (all)	1	3	0
Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	3	1	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	1 / 31 (3.23%)	2 / 31 (6.45%)
occurrences (all)	2	1	2
Teething			

subjects affected / exposed	0 / 15 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Respiratory depression			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Irregular breathing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 31 (3.23%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 31 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part A: Sugammadex 4 mg/kg	Part B: Sugammadex 2 mg/kg	
Total subjects affected by non-serious adverse events			

subjects affected / exposed	22 / 32 (68.75%)	19 / 29 (65.52%)	
Injury, poisoning and procedural complications			
Post procedural oedema			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Procedural vomiting			
subjects affected / exposed	1 / 32 (3.13%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	21 / 32 (65.63%)	11 / 29 (37.93%)	
occurrences (all)	21	12	
Procedural nausea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	3	
Teething			

subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Respiratory depression			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Irregular breathing			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Hypoxia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Postoperative wound infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2020	Major changes of Amendment (AM) 1 included allowing the use of deep endotracheal extubation in addition to awake extubation, moving "time to neuromuscular recovery" from a secondary endpoint to a primary efficacy endpoint and moving "time to extubation" from a primary endpoint to a secondary endpoint, and adding a hypothesis for "time to neuromuscular recovery".
10 January 2023	Major changes of AM 2 included a Sponsor entity name and address change and changes to the collection of "core temperature" after assessing the ERA question.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported